REMARKS

Summary of the Invention

The invention features a method of identifying an Alzheimer's disease patient who will be responsive to therapy using cholinomimetic drugs. The method involves determining the number of apoE4 gene alleles in a biological sample of the patient. The absence of apoE4 gene alleles indicates the patient will be responsive to therapy using cholinomimetic drugs.

Summary of the Office Action

Claims 1-5, 8, and 9 are under examination in the present case. Each of these claims is rejected under 35 U.S.C. § 112, first and second paragraph. The rejections are addressed below.

Support for the amendments

Support for the amendment to claims 1, 4, and 5 is found in claims 1, 4, and 5 as originally filed, and on page 27, lines 14-27 of the specification. Claim 2 is amended to provide claim language that is consistent with claim 1.

Formalities

Applicant notes that the present Office Action was made final by the Examiner in light of Applicant's amendment filed with the Reply to Office Action mailed on April 7, 2004. Applicant believes that the finality of the present Office Action is improper.

MPEP § 706.07(b) states:

> The claims of a new application may be finally rejected in the first Office action in those situations where (A) the new application is a continuing application of, or a substitute for, an earlier application, and (B) all claims of the new application (1) are drawn to the same invention claimed in the

> earlier application, and (2) would have been properly finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application...
>
> However, it would not be proper to make final a first Office action in a continuing or substitute application where that application contains material which was presented in the earlier application after final rejection or closing of prosecution but was denied entry because (A) new issues were raised that required further consideration and/or search, or (B) the issue of new matter was raised.

The amendment to claims 1, 4, and 5 submitted in the Reply to Examiner's Action dated December 16, 2002 in response to the final Office Action dated July 17, 2002 were denied entry by the Examiner on the grounds that they raise new issues that would require further consideration and/or search (see Advisory Action dated January 23, 2003). Applicant subsequently filed a Request for Continued Examination (RCE) on June 16, 2003 requesting entry of the amendment to claims 1, 4, and 5. In response, the Patent Office issued an Office Communication October 7, 2003 that indicated that the reply filed with the RCE was not fully responsive to the prior Office Action because "the wording of claim 1 had been changed such that the claimed invention differs from that examined" (Office Communication, p. 1). It is Applicant's understanding that this was a request for Applicant to provide a more complete reply to the prior Office Action and not a first Office Action on the merits.

Applicant filed a Reply to the Office Communication on April 7, 2004 amending claims 1, 4, and 5 and adding claim 9. Applicant noted in the reply that the amendments were being submitted as a *bona fide* attempt to respond to the Examiner's comments in the Advisory Action and the Office Communication. The Patent Office next issued a Notice of Non-Compliant Amendment on May 24, 2004 for failure to provide a complete listing of all of the claims and setting a one month deadline to correct the deficiency. Applicant timely filed a complete Reply to Notice of Non-Compliant Amendment on June 24, 2004.

In the present Office Action, the Examiner states:

> In response to the Non-Compliant Amendment, Applicants have filed amended claims. The Examiner still considers these claims non-compliant and indeed they add new matter to the specification...Applicants amendment necessitated the new ground(s) of rejection presented in this Office Action. Accordingly, **THIS ACTION IS MADE FINAL.**"

Office Action, pp. 2-3; emphasis in original.

Applicant respectfully submits that the finality of the present Office Action is improper because it is a first Office Action on the merits in a continuing application examining claims that were denied entry in the earlier application because they raised new issues that required further consideration and/or search (M.P.E.P. § 706.07(b)). Claims 1-5, 8, and 9, which were first submitted with the RCE filed on June 16, 2003 and amended in response to the Examiner's comments in the Office Communication, are examined for the first time on the merits, subsequent to the filing of the RCE, in the present Office Action. As is discussed above, it is Applicant's understanding that the Office Communication dated October 7, 2003 was not a first Office Action on the merits, but rather a request for Applicant to submit a completed reply to the final Office action dated July 17, 2002 in light of perceived deficiencies in Applicant's Reply to Office Action submitted with the RCE. Therefore, the present Office Action is a first Office Action on the merits examining claims that were denied entry by the Examiner in a continuing application on the grounds that they raised new issues that required further consideration and/or search. For this reason, the finality of the Office Action is improper (M.P.E.P. § 706.07(b)). Accordingly, Applicant respectfully requests that the finality of the present Office Action be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-5, 8, and 9 are rejected under 35 U.S.C. § 112, second paragraph, for lack of clarity of "failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office Action, p. 2). The Examiner states that claims 1, 4, and 5 recite "that the apoE4 allele load will be determined, and the absence of apoE4 allele identifies a subject. It is not clear what an 'apoE4 allele load' is, or how an absence of apoE4 is determined" (Office Action, p. 2).

In response, Applicant amends independent claims 1, 4, and 5 to recite that the method involves determining "whether said subject is a carrier of one or more apoE4 gene alleles," in which "a determination that said subject is a carrier of one or more apoE4 gene alleles identifies said subject as one whose Alzheimer's disease-related cognitive impairment is less responsive to treatment with a cholinomimetic drug or a determination that said subject is not a carrier of one or more apoE4 gene alleles identifies said subject as one whose Alzheimer's disease-related cognitive impairment is responsive to treatment with a cholinomimetic drug." One skilled in the art would clearly understand what is claimed and Applicants will provide an expert declaration on this point if the Examiner so desires. Because "allele load" has been removed from the claims, the rejection of claims 1-5, 8, and 9 under 35 U.S.C. § 112, second paragraph, for lack of clarity can now be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-5, 8, and 9 are rejected under 35 U.S.C. § 112, first paragraph, for adding new matter to the specification. The Examiner states:

> Claims 1-5, 8, and 9 are rejected...[for] containing subject matter which was not described in the specification in such a way as to reasonably

> convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims recite that the apoE4 allele load will be determined, and the absence of apoE4 allele identifies a subject. This method is not set forth in the specification, and is therefore new matter.

(Office Action, p. 2.) Applicant respectfully disagrees.

Applicant has amended claims 1, 4, and 5 to recite that the method involves a determination of whether a subject having AD is a carrier of one or more apoE4 gene alleles, in which a determination that the subject carries one or more apoE4 gene alleles identifies the subject as one whose AD-related cognitive impairment is less responsive to treatment with a cholinomimetic drug or a determination that the subject does not carry one or more apoE4 gene alleles identifies the subject as one whose AD-related cognitive impairment is responsive to treatment with a cholinomimetic drug. The present amendment is made to clarify the method steps recited in present claims 1, 4, and 5, and claims dependent therefrom, and the results obtained by performing the method steps.

The present amendment to claims 1, 4, and 5 finds considerable support in the specification, and thus, does not constitute new matter. Applicant directs the Examiner to claim 1, as originally filed, which states that the method involves "determining the number of copies of *apoE4* gene alleles in said subject, wherein the absence of *apoE4* gene allele in a biological sample of said subject indicates a predisposition to respond to a cholinomimetic drug." This method is based on Applicant's discovery that AD patients with one or more copies of the apoE4 gene allele respond poorly to cholinomimetic therapy, and is discussed in considerable detail on page 27, lines 14-27 of the specification, which states:

> Taken together, our data clearly suggest that cholinergic function in AD-E3/3, 3/2, and 2/2 subjects [i.e., patient lacking the apoE4 gene allele] are at least partially spared when compared to AD-E4/3, AD-E4/2, and AD-E4/4 carriers. Most importantly, this genetic susceptibility apparently

> results in subgroups of AD patients which respond differently to cholinomimetic-based therapies; with E4 carriers at a greater risk for loss of their Ach synthetic capacities. This hypothesis was formally tested in tacrine-treated AD subjects which showed different apoE genotypes. As expected, **apoE4 negative subjects were found to respond tremendously well to the acetyl-cholinersterase inhibitor tacrine (an acetylcholine metabolism enhancer) when compared to apoE4 carriers**...The presence of the apoE4 allele appears now to be the most important factor responsible for individual variations in residual brain cholinergic innervation in AD and **clearly predict clinical outcome of cholinergic based therapies**. Clinical responsiveness to cholinergic agents monitored in genotyped AD patients demonstrated that apoE4 carriers are unlikely to be good responders, at least with the use of Ach precursors and esterase-based therapies.

(Emphasis added.)

As is clear from the above passage, Applicant's specification clearly teaches that a determination of an AD patient's apoE4 genotype provides a clear prediction of the responsiveness of that patient to cholinergic based therapies. The specification states that the presence of one or two apoE4 gene alleles indicates the patient will be less responsive to cholinergic based therapies, while the absence of apoE4 gene alleles indicates the patient is likely to respond to cholinergic based therapies (Specification, page 27, lines 14-27). Thus, the subject matter of present claims 1, 4, and 5, and claims dependent therefrom, does not constitute new matter because it finds considerable support in the specification. Applicant submits that the rejection of claims 1-5, 8, and 9 under 35 U.S.C. § 112, first paragraph, for adding new matter to the specification, can now be withdrawn.

For completeness, Applicant also wishes to note that the subject matter recited in present claims 1-5 and 8-9 does not differ from the subject matter recited in previously examined claims 1-5 and 8, because the methods and the results recited in the two claim sets are the same. Both claim sets require a method step, which involves determining whether a subject having AD is a carrier of one or more apoE4 gene alleles (i.e., "determining the presence of *apoE4* gene alleles in said subject"), and a result step, which specifies that a determination that the subject does not carry one

or more apoE4 gene alleles (i.e., "absence of *apoE4* gene allele") identifies the subject as one whose AD-related cognitive impairment is responsive to treatment with a cholinomimetic drug (quoted phrases excerpted from claim 1 as filed with the Reply to Office Action dated April 30, 2002). Accordingly, the methods of present claims 1-5 and 8-9 are not separate and distinct from the methods of previously examined claims 1-5 and 8, as is asserted by the Examiner (Office Communication, p. 1). Furthermore, Applicant's amendments are not submitted to shift inventions, as is asserted by the Examiner in the Office Communication dated October 7, 2003, but rather to clarify what the Examiner indicates is a lack of clarity in the claims. The Examiner states that "it is not clear how one will know if an allele is not present, because it would not be present in the determination of apoE4 alleles" (Office Communication dated October 7, 2003, p. 1). Applicant believes that the present amendment to claims 1, 4, and 5 clearly and concisely sets forth the claimed invention, does not render the scope of present claims 1-5 and 8-9 separate and distinct from the scope of previously examined claims 1-5 and 8, and should alleviate the Examiner's confusion regarding performance of the methods of present claims 1-5 and 8-9.

Obviousness-Type Double Patenting

Claims 1-5, 8, and 9 are rejected for obviousness-type double patenting over claims 1-4 of U.S. Patent No. 5,935,781 ('781 patent). Applicant will submit a terminal disclaimer in compliance with 37 C.F.R. 1.321(c), if appropriate, once notice of otherwise allowable subject matter is received.

CONCLUSION

Applicant submits that the claims are in condition for allowance and such action is respectfully requested. The courtesy of a telephone interview is requested, should the Examiner reach a different conclusion.

Enclosed is a petition to extend the period for replying for three months, to and including February 16, 2005.

If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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